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Establishment of a Clinically Relevant Blunt Injury Swine Model for Extremity Compartment Syndrome

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DISTRIBUTION STATEMENT A - Approved for public release; distribution is unlimited.

13. SUPPLEMENTARY NOTES

Report contains tables.

14. ABSTRACT

This document is the Final Report of the Establishment of a Clinically Relevant Blunt Injury Swine Model for Extremity Compartment Syndrome project funded by AFMSA/SG9S contract AFDW-2011-002A. This Final Report discusses the successful completion of the program objectives.

15. SUBJECT TERMS

Extremity Compartment Syndrome. Intramuscular Pressure. Mean Arterial Pressure. Serum Myoglobin. Creatinine Kinase. Lactic Acid.

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Final Report

30 September 2011

1. Type of Research: Animal research

2. Title: Establishment of a clinically relevant blunt injury animal model for extremity compartment syndrome in the adult swine (*Sus scrofa*).

3. Principal Investigator (PI):

Julio Lairet, Maj, USAF, MC

4. Purpose:

Extremity injuries are the most common injury reported from the current conflicts in Iraq and Afghanistan. Between January of 2005 and August of 2006 Ritenour, et al reported seventy-three patients required 177 fasciotomies with 85% carrying the diagnosis of Extremity Compartment Syndrome (ECS) in Germany after transport. ECS is the result of an increase in intramuscular pressure (IMP) due to an increase in intramuscular fluid, either due to edema or hemorrhage. As fluid increases the pressure within the compartment that contains the muscle(s) increases. As this occurs IMP may exceed myoneural capillary perfusion pressure, severely limiting or halting blood flow, resulting in tissue ischemia. Pearse et al. defined acute compartment syndrome as "a surgical emergency characterized by raised pressure in an unyielding osteofascial compartment" that can be caused by trauma, revascularization procedures, or exercise. While the exact IMP at which acute compartment syndrome occurs is debated, it is generally accepted that it occurs when the IMP increases to within 30 mm Hg of mean arterial pressure (MAP). The relationship between blood pressure and IMP is critical in the case of battlefield trauma in which blood pressure is often lowered due to hemorrhage, i.e., compartment syndrome occurs at a lower IMP in a hypotensive patient.

Anatomical features of certain muscles make them particularly susceptible to ECS; these features include a thick, relatively noncompliant fascia and proximity to bones, both contributing to the inability of the muscle to expand adequately in the face of fluid accumulation. Currently the available animal models of ESC are limited. The currently available large animal models of ECS involve either the infusion of fluids into the anterior compartment to raise IMP, or use a balloon catheter placed between the tibia and the muscles of the anterior compartment of the lower limb that increases IMP when inflated. These methods are effective in dramatically raising IMP, but their clinical relevance is limited in as much as they do not simulate the actual pathology that causes ECS, therefore it is not a clinically relevant injury model.

Due to the nature of the injuries in a wartime environment, it is important to have an animal model that takes into account the mechanism of injury such as blast and blunt trauma. Such a model will enable us to better understand the physiology of what occurs during ECS and implement potential strategies where this condition may be adverted.

The objective of this protocol is to develop a blunt trauma clinically relevant large animal model for ECS.

5. Hypothesis

The objective of this study is to establish a large animal clinically relevant model to study extremity compartment syndrome induced by blunt trauma.

6. Results:

The average weight of the subjects was 63 kg (range 60 to 67 Kg). ECS as defined IMP within 30 mm Hg of the MAP was reached in 86% (6/7) of the swine in experiment 4 and 100% (7/7) of the swine of experiment 5.

	Mean MAP (mmHg)	Mean IMP injured leg (mmHg)	Mean IMP control leg (mmHg)	Mean high IMP injured leg (mmHg)	Mean time (min) with IMP of injured leg consistent with ECS*	Developed ECS by definition*
Experiment 4	62 (50-75)	21 (13-33)	9 (4-16)	32 (25-44)	273 (0-1415)	6/7 (86%)
Experiment 5	65 (56-82)	19 (12-36)	10 (0-23)	35 (18-76)	289 (60-1140)	7/7 (100%)

A comparison of mean MAP, IMP, and high IMP between experiments 4 and 5
*** IMP within 30 mm Hg of mean arterial pressure (MAP)**
Table 1

When assessing the tissue pathology a greater degree of inflammation was seen in tissue samples from the injured extremity from experiment 5 when compared to tissue samples from experiment 4 (mild versus minimal), no inflammation was noted in any of the control legs for either experiment. These findings were most likely due to the result of the increased observation time in experiment 5 (48 hours) versus experiment 4 (24 hours) and a key factor in the development of ECS. The same degree of tissue apoptosis was present in the injured legs of both experiments without any evidence of apoptosis noted in the control legs. When evaluating for the presence of tissue necrosis; a greater degree of necrosis was noted in experiment 5 versus experiment 4 (table 2).

Experiment 4	Experiment 5
57% of subjects had 20-40% necrosis	86% of subjects had 20-40% necrosis
29% of subjects had 5-20% necrosis	14% of subjects had 5-20% necrosis
14% of subjects had 0-5% necrosis	

A comparison presence of tissue necrosis between experiments 4 and 5
Table 2

Review of the tissue by the veterinary pathologist revealed that the second group (experiment 5) clearly had a larger average area of necrosis (19% increase) and degeneration (24% increase) and higher average inflammatory (66% increase) and edema (14% increase) scores when compared to samples from experiment 4. We believe that the increase in inflammatory score was primarily driven by time. The additional 24 hours in experiment 5 allowed more time for neutrophils to appear in the wound.

Review of the chemistry data reveals that shock was achieved during the hemorrhage portion of the experiment as planned (table 3 and 4). The serum lactate increased in both experiments from baseline to 1 hour post-hemorrhage. As predicted the serum lactate then decreased after the resuscitation was initiated.

The serum myoglobin and creatinine kinase (CK) both rose throughout the experiment as expected. The development of ECS will yield high CK and myoglobin levels. The higher increase in myoglobin and CK in experiment 5 when compared to experiment 4 was most likely due to using only blood as part of the resuscitation in experiment 5. In experiment 4 crystalloids and blood were administered as part of the resuscitation.

	Baseline	1hr post-hemorrhage	1hr post-resuscitation	24 hours
Serum Myoglobin (ng/ml)	45	72	77	493
CK (U/L)	962	698	886	3003
Lactic Acid (mmol/L)	1.6	2.4	1.2	0.8

Mean chemistry results for experiment 4
Table 3

	Baseline	1hr post-hemorrhage	1hr post-resuscitation	24 hours	48 hours
Serum Myoglobin (ng/ml)	35	73	128	1081	1356
CK (U/L)	638	676	950	20309	21265
Lactic Acid (mmol/L)	1.7	5	4	0.6	2.8

Mean chemistry results for experiment 5
Table 4

Review of the data supports the conclusion that we have successfully established a clinically relevant large animal model to study extremity compartment syndrome induced by blunt trauma. Extending the experiment to 72 or 96 hours could yield more tissue changes relevant to the pathophysiology of ECS.

7. How may your findings benefit the Air Force?

The findings of this study support the use of this model to study ECS induced by blunt injury to include variables which may be contributing factors in the establishment of ECS as well as possible mitigating interventions and thus potentially decrease the incidence of ECS.

8. Status of Funds:

Funds received: $98,621.00 - All funds have been allocated.

9. Reason for Closure:

Objectives of the study were met

10. Specific Problems:

None

11. Publications and Presentations:

The manuscript is in development – when accepted for publication a copy will be forwarded to AFMSA/SG9S. An abstract will be submitted for presentation at the Air Force Medical Services 2012 Research Symposium as well as the 2012 Annual Meeting of the American College of Emergency Physicians. If accepted for presentation AFMSA/SG9S will be notified.

All publications will be cleared by 59MDW Public Affairs prior to submission.

12. Exceptional Achievements:

None

13. Signature of Principal Investigator:

Julio Lairet, Maj, USAF, MC
Director of Enroute Care Research Center